

PANCREATIC VEIN CATHETERIZATION WITH GASTRIN ASSAY IN NORMAL PATIENTS
AND IN PATIENTS WITH THE ZOLLINGER-ELLISON SYNDROME.

Stig Ingemansson¹, M.D., Lars-Inge Larsson², M.D.,
Anders Lunderquist³, M.D. and Flemming Stadil⁴, M.D.

Departments of Surgery¹ and Diagnostic Radiology³, University of Lund,
S-221 85 Lund, Sweden. Institue of Medical Biochemistry², University
of Aarhus, Aarhus, and Department of Surgery⁴, Herlev hospital, Copen-
hagen, Denmark.

Abstract

Simultaneous catheterization of the aorta and the caval, portal and pancreatic veins with blood sampling for gastrin radioimmunoassay was performed in three patients with the Zollinger-Ellison syndrome and in five control patients without peptic ulcer disease. In the controls the gastrin concentrations in the pancreatic veins ranged from 15 to 148 pg/ml ($\bar{m}$ = 65, median = 67). Pre- and postoperative catheterizations were performed in two of the Zollinger-Ellison patients and very high gastrin concentrations in several pancreatic veins indicated the occurrence of multiple tumors whereas angiography was able to reveal only one tumor in one of the patients. Twelve months after extirpation of the tumors and total gastrectomy, gastrin concentrations in peripheral as well as in pancreatic venous blood were lower but still pathologically high. The third patient was catheterized twice; two and twelve months after tumor extirpation and total gastrectomy. The gastrin values from this patient were within the range of the reference group except for one pancreatic vein with slightly increased concentrations. The gastrin concentration did not increase in the interval between the two catheterizations. No complications were noted. The tripple catheterization technique with blood sampling for hormone assay is advocated for as a diagnostic tool and as a localization procedure in patients with proven or suspected Zollinger-Ellison syndrome.

In 1955 Zollinger and Ellison described a syndrome characterized by gastric hyperacidity, recurrent peptic ulcerations and pancreatic islet cell tumors (1). The syndrome was later found to be caused by gastrin producing tumors - gastrinomas (2). Ultrasound (3), scintiscan (4), pancreatic phlebography (5) and arteriography (6,7) are methods used preoperatively to localize pancreatic endocrine tumors. The best method - arteriography - has an accuracy of 40-60% (6,7). During operation, inspection, palpation and biopsy techniques may be used. The tumors are frequently multiple and malignant (8,9), which makes radical surgery difficult or impossible. Since no reliable localization procedure is available it is difficult or impossible to evaluate whether single or multiple tumors are present. Because of this, treatment is often concerned with the target organ - the stomach (8,9,22,23). New procedures have to be found and tested in order to localize the tumors preoperatively, assess radicality postoperatively and provide early localization of recurrences. We have reported on simultaneous caval, aortal and portal vein catheterization combined with selective pancreatic and intestinal vein catheterization with blood sampling for hormone assay in patients with insulinoma (10), islet cell hyperplasia (11) and glucagonomas (12).

The aim of the present work was to investigate:

1. whether simultaneous caval, aortal and pancreatic vein catheterization with blood sampling for gastrin assay was possible to perform before and after extirpation of tumors and total gastrectomy in patients with the Zollinger-Ellison syndrome.
2. if pathologically high, pancreatic, arterio-venous gastrin differences could be used for localization of gastrin producing tumors.

Material

Two females and three males, 27-64 years old, without peptic ulcer disease or gastric hypersecretion were catheterized. These patients were used as a reference group (referred to as number A, B, C, D and E).

Three patients, one male aged 55 years (referred to as patient no I) and two females aged 34 and 38 years (patients no II and no III, respectively) with the Zollinger-Ellison syndrome (Table I) were catheterized. Patient no I and patient no II were catheterized both preoperatively and twelve months postoperatively. After preoperative catheterization patient no I underwent tumor extirpation and in a second operation total gastrectomy since he developed a perforated duodenal ulcer. Patient no II underwent surgery including tumor extirpation and total gastrectomy. Patient no III had earlier been operated twice due to perforated jejunal ulcers. She was admitted to our department because of ileus and had an acute operation. Due to extreme gastric retention postoperatively an acute gastrectomy combined with extirpation of the

tumor was carried out. This patient was catheterized two months and twelve months after the gastrectomy.

Methods

Following eight hours of fasting percutaneous transhepatic catheterization of the portal vein was performed simultaneous with percutaneous catheterization of the inferior v. cava and the aorta via femoral vein and the femoral artery respectively. Blood samples were withdrawn from different aortal and caval branches for hormone assay in order to localize possible extrapancreatic tumors. Subsequently the caval catheter was placed in the hepatic vein and the aortic catheter in the coeliac artery. The portal catheter was used for catheterization of different pancreatic and intestinal veins and blood was withdrawn for hormone assay. To assess the exact localization of the tip of the catheter through which the blood samples were withdrawn a series of films were taken in most cases after handinjection of contrast medium (11,12).

After centrifugation of the blood samples sera was stored at -20°C until assayed.

Serum concentrations of gastrin were determined by radioimmunoassay (antiserum 2604) as described earlier (13,14). With the technique employed all four main components of circulating gastrin were measured with almost equimolar potency. During each operations specimens taken from the tumors were frozen to the temperature of liquid nitrogen in a propane-propylene mixture, freeze-dried and fixed in the vapors of either paraformaldehyde or diethylpyrocarbonate and embedded in paraffin. Deparaffinized $3\mu\text{m}$ thick sections were subjected to an indirect immunocytochemical method for the demonstration of gastrin, glucagon, insulin, human pancreatic polypeptide (HPP) or vasoactive intestinal polypeptide (VIP) as described elsewhere (15,16,17). The site of antigen-antibody reaction in the tissue sections was revealed with either immunofluorescence or the PAP method of Sternberger (18).

The statistical methods used were analysis of variance and analysis of regression.

Results

The preoperative diagnosis of patients I, II and III were based on peptic ulcer disease, hypersecretion and in patients I and II also on the presence of hypergastrinemia and glucagon induced gastrin release.

Table I.

Pre- and peroperative findings in 3 patients with Zollinger-Ellison syndrome.

<u>Patient no I</u>		<u>Patient no II</u>	<u>Patient no III</u>
		<u>Preoperative findings</u>	
Scintiscan	Normal	Normal	Not performed
Angiography	2,5 x 1,5 cm large tumor in the pancreatic head.	Normal	Not performed
Portal phlebography	Normal	Normal	Not performed
Pancreatic phlebography	Normal	Normal	Not performed
Tripple catheterization with gastrin assay	Tumors in the head and body of the pancreas (Fig. 1 a)	Tumor gastrin drainage from the pancreatic gland (Fig. 2 a)	Not performed
		<u>Peroperative findings</u>	
Palpation and inspection	Multiple tumors in the duodenal wall, in the pancreatic head, in the pancreatic body, local lymphnodemetast. No livermetast.	Tumor in the pancreatic body, local lymphnodemetast. No livermetast.	One tumor in the body of pancreas, no lymphnodemetast. No livermetast.
Immuncytochemistry	Gastrinoma	Mixed tumor producing gastrin and HPP	Gastrinoma

Table III.

Change in gastrin concentrations in different vascular areas during the tripple catheterization procedure in patient no. I, II and III. (n = number of samples, b = regression coefficient, r = correlation coefficient).

		n	b	r	P
Pat. I	A. coel. (preop.)	3	2.77	0.88	n.s.
	(postop.)	3	0.486	0.15	n.s.
	V. hep. (preop.)	3	0.846	0.58	n.s.
	(postop.)	3	0.171	0.19	n.s.
Pat. II	A. coel. (preop.)	9	9.595	0.790	0.05 *
	(postop.)	4	7.333	0.937	n.s.
	V. hep. (preop.)	9	1.754	0.278	n.s.
	(postop.)	4	0.333	0.443	n.s.
Pat. III	V. hep. (postop. 2 months)	8	0.56	0.8156	<0.05 *
	V. hep. (postop. 12 months)	8	0.521	0.8482	<0.01 **

Table II.

Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during catheterization of 5 patients without the Zollinger-Ellison syndrome (referred to as patients A, B, C, D and E).

Pat. no	A. coel.					V. hep.					V. port. centr.					V. pancreat.					
	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E	
Sample no																					
1	69	58	17	84	46	77	79	25	81	41	77	56	30	66	63	PSPD			58	88	72
2	50	60	27	36	70	73	68	15	35	56	76			50	83	ASPD	60	91	32		
3	66	40	14	29	86	65	44	14	35	66	82				113	GCT	68		30		
4	82	37	28	40	52	83	54	26	43	44	86					GCT	68				
5	77		19			83	43	25	52	58						DP	90	54	15	33	66
6			14			71	49	12		34						DP	98			69	
7			13				44	28		46						DP	130			148	
8			22					20								DP	143			135	
9			17					29								DP	134			47	
10			11					28								v. transv.			36		
11			29					20								v. transv.			42		
12			32					19								v. pancreat.			59		
																v. pancreat.			55		
																v. coronar.	66		19		

The results of scintiscan, portography, pancreatic phlebography, arteriography and the peroperative findings are shown in table I.

Reference group

Serum gastrin concentrations in the reference group are shown in table II. Peripheral gastrin concentrations were within the normal range (<100 pg/ml) in this group (14). Pancreatic vein gastrin concentrations ranged between 15 and 148 pg/ml ($\bar{m} = 65$ /ml, median = 67 pg/ml). The concentrations were higher in the pancreatic veins than in the coronary veins (table II).

Zollinger-Ellison group

In patient no I preoperative catheterization revealed abnormal high gastrin concentrations in all three vascular areas (fig. 1 a). The highest values were found in or close to the veins draining the pancreatic head and the duodenal loop (fig. 1 a, sample no 5,6,7). One high value in the splenic vein was found close to the vein draining the pancreatic body (fig. 1 a, sample no 2). In this region no pancreatic vein could be catheterized selectively. The coronary vein contained only 201 pg/ml. During operation several tumors were removed from the duodenal wall and a tumor situated in the pancreatic head, a tumor in the pancreatic body and a large lymph node metastasis in the groove between the pancreatic head and the second part of the duodenum were also removed. The site of the metastasis agreed with the arteriographic findings. A cystic lesion in the proximal part of the pancreatic tail was also found and removed. No liver metastases were seen or palpated.

Tripple catheterization 12 months after the operation revealed a significant ($p < 0.001$) decrease in concentrations of gastrin (fig. 1 a,b) but all values were still above those of the reference group. The highest portal gastrin value was found in the transverse pancreatic vein (fig. 1 b, sample no 4,5). The gastrin concentrations in the coeliac artery and the hepatic vein did not change significantly during the pre- or postoperative investigations (Table III).

In patient no II abnormal high gastrin values were found in all three vascular areas (fig. 2 a) at the preoperative catheterization. The highest values were found in the upper portion of the superior mesenteric vein and in the main stem of the portal vein (fig. 2 a, sample no 8,10), the lowest in the coronary vein.

At explorative laparotomy two pancreatic tumors were found and extirpated, one from the head and one from the body. Two lymph node metastases were removed from the upper part of the pancreatic body. No liver metastases were detected.

Gastrin pg/ml		
1. v. lienal.	= 424	v. hep = 532 a. coel = 432
2. v. lienal.	= 612	v. hep = 492 a. coel = 520
3. GCT	= 444	
4. v. portae	= 604	v. hep = 552 a. coel = 560
5. v. mes. sup.	= 720	
6. v. ASPD	= 776	
7. v. portae	= 712	
8. v. coronar.	= 201	

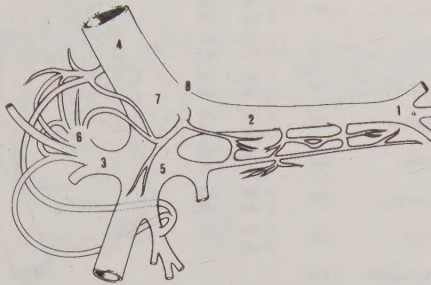


Fig. 1 a. Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during preoperative catheterization of patient no I.

Gastrin pg/ml		
1. v. mes. sup.	= 340	v. hep = 328 a. coel. = 240
2. v. port. confluens	= 264	
3. v. mes. sup. dist.	= 280	
4. v. pancreat. transvers.	= 400	
5. v. pancreat. transvers.	= 464	v. hep. = 304 a. coel. = 328
6. v. portae centr.	= 332	
7. v. portae centr.	= 312	
8. v. portae centr.	= 372	v. hep. = 328 a. coel. = 244

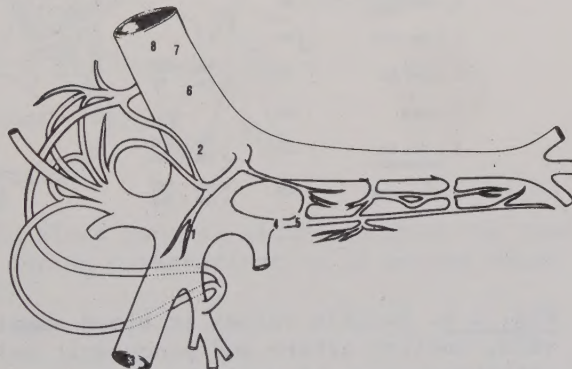


Fig. 1 b. Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during postoperative catheterization of patient no I.

Gastrin pg/ml		
1. v. lienal.	= 1720	v. hep. = 1840 a. coel. = 1280
2. v. lienal.	= 1720	v. hep. = 1660 a. coel. = 1460
3. v. mes. inf.	= 1540	v. hep. = 1860 a. coel. = 1680
4. v. lienal.	= 1700	v. hep. = 1680 a. coel. = 1600
5. v. coronar.	= 1280	v. hep. = 1640 a. coel. = 1400
6. v. PSPD	= 1560	v. hep. = 1760 a. coel. = 1500
7. v. portae	= 1600	v. hep. = 1760 a. coel. = 1700
8. v. mes. sup.	= 2380	v. hep. = 1920 a. coel. = 1840
9. v. ASPD	= 1700	v. hep. = 1760 a. coel. = 1760
10. v. portae centr.	= 2280	

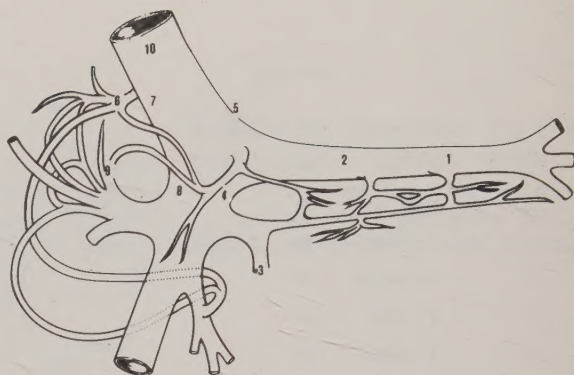


Fig. 2 a. Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during preoperative catheterization of patient no II.

Gastrin pg/ml		
1. v. transv. pancreat.	= 760	
2. v. lienal.	= 1000	
3. v. lienal.	= 950	v. hep. = 905 a. coel. = 800
4. v. mes. inf.	= 850	
5. v. port. confl.	= 900	
6. v. mes. sup.	= 900	v. hep. = 1020 a. coel. = 980
7. v. porta	= 1020	
8. v. mes. sup. (outside GCT)	= 1120	v. hep. = 1100 a. coel. = 1080
9. v. port. centr.	= 1120	v. hep. = 1150 a. coel. = 1040

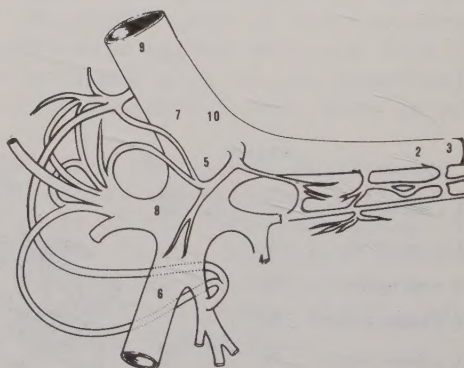


Fig. 2 b. Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during postoperative catheterization of patient no II.

Gastrin pg/ml		
1. v. ilenal. dist.	= 81	v. hep. = 91 a. coel. = 80
2. v. ilenal.	= 86	v. hep. = 97 a. coel. = 86
3. v. pancreat. dist.	= hemolysis	
4. v. ilenal.	= 95	v. hep. = 106 a. coel. = 98
5. v. ilenal.	= 102	v. hep. = 113 a. coel. = 113
6. v. portae	= 128	v. hep. = 117 a. coel. = 120
7. v. ASPD	= 201	v. hep. = 102 a. coel. = 105
8. v. mes. sup.	= 116	v. hep. = 120 a. coel. = 118
9. v. mes. sup.	= 131	
10. v. port. confl.	= 114	
11. v. port. centr.	= 117	v. hep. = 133 a. coel. = 117

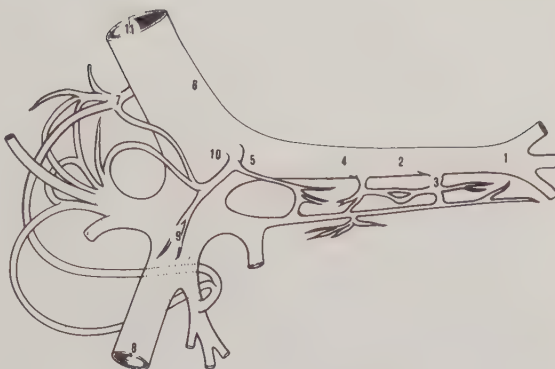


Fig. 3 a. Gastrin values in blood samples withdrawn from the caval vein, coeliac artery and pancreatic veins during catheterization 2 months after operation of patient no III.

Gastrin pg/ml		
1. v. pancreat. transv.	= 109	
2. v. pancreat. transv.	= 115	v. hep. = 131
3. v. port. confl.	= 120	v. hep. = 131
4. v. port. confl.	= 112	
5. v. port. confl.	= 116	
6. v. port. centr.	= 130	v. hep. = 142



Fig. 3 b. Gastrin values in blood samples withdrawn from the caval vein and pancreatic veins during catheterization 12 months after operation of patient no III.

Twelve months postoperatively pathologically high, although lower concentrations of gastrin ($p < 0.001$) were still found in all three vascular areas (fig. 2 b). However, the values in the portal system did not differ from those of the coeliac artery samples. The highest values were found in the upper portion of the superior mesenteric vein and in the main stem of the portal vein. The gastrin concentrations in the coeliac artery and the hepatic vein did not change significantly during the pre- or postoperative investigations (Table III).

At the operation of patient no III only one pancreatic tumor localized in the body of the pancreas was palpated and extirpated. No lymph node or liver metastases were found upon inspection or palpation. Total gastrectomy and splenectomy was also performed. Two months following the operation tripple catheterization revealed normal gastrin concentration in the three vascular areas (fig. 3 a). The highest value was found in the ASPD-vein (fig. 3 a, sample no 7). Twelve months after operation re-catheterization revealed unchanged gastrin concentrations (fig. 3 b). The ASPD-vein however, could not be catheterized this time. The highest pancreatic vein gastrin concentration was well within the range of the reference group (fig. 3 a, table II). The gastrin concentration did raise during the first investigation in the hepatic vein ($p < 0.05$) and during the second investigation in the hepatic vein ($p < 0.01$) (Table III).

Tissue analyses

All three tumors showed mostly a trabecular growth pattern but in some areas it was nodular. Immunocytochemical analyses revealed that all the tumors contained numerous strongly gastrin immunoreactive cells. In each case such cells made up more than 80 per cent of the total tumor cell population. The tumor of patient no II contained in addition a few scattered HPP immunoreactive cells. HPP cells were not seen in the tumors of patient no I and III. All tumors were devoid of insulin, glucagon and VIP immunoreactive cells.

Discussion

In most patients the gastrin levels seen in the coronary veins were lower than in the pancreatic veins. This findings is hardly surprising in the gastrinoma patients since their antral gastrin release may well be suppressed by acid hypersecretion. Further, the fundic portion of the stomach has been suggested to remove significant quantities of gastrin from the circulation - an observation in accordance with our finding of lower levels of gastrin in the coronary veins than in the coeliac artery. Surprisingly, however, also in some patients of our reference group the pancreatic venous blood was richer in gastrin than

that of the coronary veins. However, these observations were made in the fasting state and should therefore be interpreted with care. Observing this precaution two different explanations may be offered. First, presumably most of the antral venous effluent is not delivered to the coronary veins but instead to short gastric veins and to the gastroduodenal trunk (GDT). Another possibility is that gastrin immunoreactive substance are secreted by the normal pancreas itself. The D-cells of the pancreatic islets have repeatedly been reported to contain a gastrin immunoreactive material (15,16,20). It has, however, been convincingly shown that, if present, this material differs substantially from gastrin occurring in antrum, duodenum and Zollinger-Ellison tumors (17). Likewise pancreatic gastrinomas are not D-cell tumors but often contain cells similar to the G-cells. Such cells have recently been detected in pancreatic tissue from the foetal and neonatal rats but the cells were absent from the adult pancreas (19,21). The occurrence of true gastrin cells during foetal and neonatal life may possibly explain why pancreatic gastrinomas occur. In addition, a gastrin immunoreactive material, distinct from known forms of gastrin may be secreted from the adult human pancreas. The nature and biological function of this putative material is as yet unknown.

Gastrinomas are difficult to localize pre- and peroperatively and the main purpose of this study was to develop an investigatory procedure which permitted preoperative localization. It has been shown that pancreatic endocrine tumors causing hyperinsulinemia or hyperglucagonemia can be localized by the marked arterio-venous differences in hormone concentrations (10,11,12) and subsequently extirpated on basis of the venous anatomy and the knowledge of the hormone concentrations. Radical extirpation is then possible but has hitherto been difficult in the Zollinger-Ellison syndrome where total gastrectomy has been the accepted method of treatment (6,22,23). However, total gastrectomy has disabling side effects. Previous attempts at medical treatment have been negative but the advent of histamin H_2 -receptor antagonists which inhibit acid secretion (24,25) have raised new possibilities. Combined with a preoperative accurate localization procedure the extirpation of tumors may now be attempted and if successful will be the therapy of choice also in patients with gastrinomas.

Conclusions

1. Simultaneous catheterization of the vena cava, aorta and pancreatic veins with blood sampling for hormone assay is possible to perform both before and after tumor extirpation and total gastrectomy in patients with the Zollinger-Ellison syndrome.
2. Gastrin concentrations in the three vascular areas indicate the area into which the tumor drains, and thus can exclude the presence of extrapancreatic tumors.

3. Extremely high gastrin concentrations in several pancreatic veins seem to indicate multiple tumors and/or lymph node metastases even when arteriography is normal.

The tripple catheterization technique may be a valuable adjunct to more conventional, morphological localization procedures in patients with suspected or proved Zollinger-Ellison syndrome.

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